DATA EVALUATION RECORD

1-METHYLCYCLOPROPENE
OPPTS 870.7485 ([' 85-1)]; OECD 417)
STUDY TYPE: TOXICOKINETIC - RAT
MRID 47088616

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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Task Order No. 07-042

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - [Rat]; OPPTS 870.7485 [' 85-1)]; OECD 417.

PC CODE: Not provided **DP BARCODE:** 339928

TEST MATERIAL (PURITY): 1-Methylcyclopropene alpha-cyclodextrin complex (3.4% a.i.)

SYNONYMS: SmartFresh™

CITATION: Hazelton, G.A. and R.E. Swenson. (2007). ^{14}-C-1-Methylcyclopropene: Toxicokinetic study in rats. Rohm and Haas Co., Toxicology Dept. 727 Norristown Road, P.O. Box 904, Spring House, PA 19477-0904. Report No. 01R-004E. January 31, 2007. MRID 47088616. Unpublished.

SPONSOR: Rohm and Haas Co., Toxicology Dept. 727 Norristown Road, P.O. Box 904, Spring House, PA 19477-0904

EXECUTIVE SUMMARY:

In a toxicokinetic study (MRID 4708816), 1-methylcyclopropene (1-MCP) in an alpha cyclo-dextrin complex (3.16% a.i., (sublots of Lot No. 1034.00 labeled on carbon 3 of the ring) was administered to groups of three male and three female cannulated Crl:CD®BR rats by inhalation at concentrations of 100 ppm or 1000 ppm (equivalent to 221 and 2212 mg/m^3 or 0.221 or 2.212 mg/L, respectively) for four hours. During exposure, whole blood and/or plasma samples were collected. At the end of exposure, three male and three female rats exposed to 1000 ppm were sacrificed. Three rats/sex/ exposure group were placed into metabolism cages and additional blood samples were drawn until 20 hours after exposure. At sacrifice, the liver, kidney, spleen, lungs, and fat were collected and the amount of radioactivity determined in these tissues and organs, as well as the residual carcass of all rats in the study.

Absorption was similar between the sexes within exposure groups with rats exposed to 100 ppm having ~5% of the dose in the tissues or excreta while rats exposed to 1000 ppm had ~1.9% 20 hours after treatment. Tissue distribution was also similar between sexes within exposure groups; with specific tissue accumulation <0.5% of the exposure dose and residual carcass concentrations <2% at both exposure concentrations. No bioaccumulation was noted. Concentrations of the radiolabel in the excreta were low, implying limited absorption, but were higher in the urine than the feces. No significant differences in elimination were found between the sexes within exposure groups.

^{14}C-1-MCP was detectable in the whole blood and plasma of male and female rats within 15 minutes of exposure with concentrations generally increasing in a linear fashion and peaking at the end of the four-hour exposure. The concentrations of the radiolabeled test material in the whole blood and plasma of male and female rats were low in both exposure groups. In male and female rats treated with 100 ppm or 1000 ppm, similar concentrations of radiolabel in the whole blood and plasma and similar T_{max}, C_{max}, and $T_{½}$ values were found; implying similar absorption between the sexes. The results between whole blood and plasma values suggest that the radiolabeled test material was carried in the plasma with little binding to the red blood cell. In Group 3 female rats, elimination from the plasma and blood appeared bi-phasic. Differences in AUC between the two exposure groups suggest absorption was approaching saturation at 1000 ppm. The relatively long $T_{½}$ in both sexes at both exposure concentrations suggest that elimination is somewhat slow. No assumptions regarding the metabolic disposition of the test material can be made based on the study results.

This metabolism study in the Crl:CD®BR rat is classified **Unacceptable/Nonguideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in the rat. The study does provide useful information about the toxicokinetics of radiolabeled 1-methylcyclopropene.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test compound:

Radiolabelled test material: ^{14}C-1-Methylcyclopropene (^{14}C-1-MCP) alpha-cyclodextrin complex (labeled on carbon 3 of ring)

Radiochemical purity: 94.9%; 3.16%, 3.16% a.i. radiolabel in complex (method not reported but assumed GC

Specific activity: 3.03 mCi/g (specific activity of the radiolabeled gas – 87.0 mCi/g)

Lot/batch #: Lot Nos. 1034.0001 and 1034.0005 (sublots of 1034.00)

Non-Radiolabelled test material: 1-Methylcyclopropene (1-MCP)

Description: 1-MCP is encapsulated in alpha-cyclodextrin and released as a gas with addition of water

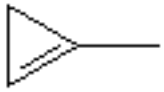
Lot/batch #: BAS 5-80

Purity: 3.4% a.i. (method not reported but assumed GC)

Contaminants: Not reported

CAS # of TGAI: 3100-04-7

Structure:



2. Vehicle: None

3. Test animals:

Species: Rat

Strain: Crl:CD®BR (all rats were jugular cannulated)

Age/weight at study initiation: 8-10 weeks (221-336 g)

Source: Charles River Laboratories, Portage, MI.

Housing: Metabolism cages (following exposure)

Diet: PMI Certified Rodent Diet 5002, *ad libitum*

Water: Tap water, *ad libitum*

Environmental conditions: Not reported

Acclimation period: 3-7 days

4. Preparation of dosing solutions:

B. STUDY DESIGN AND METHODS:

1. Group arrangements

The rats were ordered in a staggered sequence and randomly assigned to the groups shown in Table 1 by use of a computerized data collection system (further details of group assignment were not provided).

TABLE 1: Exposure concentrations of toxicokinetic studies of male and female rats for 1-methylcyclopropene					
Group	Exposure Concentration			Number/sex (M/F)	Remarks
	ppm	mg/m^3	mg/L		
Control	1000	2212	2.21	2/0	Two male rat carcasses were exposed to the radiolabeled test material for four hours to determine the amount of activity adhering to the skin and/or fur. The samples were collected at 0.25, 0.5, 0.75, 1, 2, 3, and 4 hours during exposure.
1	1000	2212	2.21	4/2	Whole blood was collected at 0.25, 0.5, 1, 2, 3, and 4 hours during exposure. The rats were killed after four hours of exposure and the carcasses frozen for the determination of ^{14}C.
2	100	221	0.22	3/3	Whole blood and plasma were collected 1, 2, 3, and 4 hours during exposure and at 8 and 24 hours after the start of exposure (4 and 20 hours after exposure). After the four-hour exposure, the rats were placed into metabolism cages and urine and feces collected over dry ice. At 24 hours after the start of exposure, the rats were killed and the liver, kidney, spleen, lung, fat, and remaining carcass collected for ^{14}C analyses.
3	1000	2212	221	2/0	Whole blood and plasma were collected 0.25, 0.5 1, 2, 3, and 4 hours during exposure and at 8, 12, and 24 hours after the start of exposure (4, 8, and 20 hours after exposure). At the end of the four-hour exposure, the rats were placed into metabolism cages and urine and feces collected over dry ice. At 24 hours after the start of exposure, the rats were killed and the liver, kidney, spleen, lung, fat, and remaining carcass collected for ^{14}C analyses. (Data from Group 3 and 3A rats were combined for analysis and the results reported as Group 3.)
3A	1000	2212	221	1/3	Whole blood and plasma were collected 1, 2, 3, and 4 hours during exposure and at 8 and 24 hours after the start of exposure (4 and 20 hours after exposure). At the end of the four-hour exposure, the rats were placed into metabolism cages and urine and feces collected over dry ice. At 24 hours after the start of exposure, the rats were killed and the liver, kidney, spleen, lung, fat, and remaining carcass collected for ^{14}C analyses. (Data from Group 3 and 3A rats were combined for analysis and the results reported as Group 3.)

Data from page 14 of MRID 47088616

2. Dosing and sample collection:

a. Exposure procedure: Since 1-methylcyclopropene (1-MCP) is a vapor, the appropriate amount of radiolabeled test material was weighed into glass bottles containing stir bars and the bottle sealed with an air tight septum. The radiolabeled atmosphere was generated by injecting 2 mL of purified water into each bottle and the bottle placed on stir plates to release the radiolabeled atmosphere. Triplicate 100 µL aliquots of each stock atmosphere were taken with a gas tight syringe just prior to exposure and injected into the head space of septum-sealed glass vials containing Ultima Gold™ scintillation fluid. The vials were analyzed by LSC to determine the appropriate amount of stock solution required to spike each rat exposure chamber with the radiolabel.

The rats were exposed to atmospheric concentrations of 100 ppm or 1000 ppm radiolabeled test for four hours. Each rat was secured in a restrainer and placed into individual chambers consisting of a 60L Tedlar gas sampling bag supported by a steel frame. A glass dish containing unlabeled 1-MCP and a stir bar was inserted into the bag and the bag sealed. Each exposure bag had two septum sealed sampling ports, as well as a stainless steel port. The blood catheter was threaded throughout the stainless steel port and the port sealed with a silicone adhesive. Warmed purified water was injected

through a polypropylene sampling port into the glass dish containing 1-MCP and the mixture stirred to release the vapor. The bag was spiked with an injection of the appropriate volume of radiolabeled 1-MCP stock atmosphere. Test chamber atmosphere samples were taken throughout the exposures at one hour intervals with a gas tight syringe and analyzed by GC to verify target concentrations of 1-MCP.

b. Pharmacokinetic studies: Whole blood samples were drawn from the cannulated rats of Group 1 through Group 3A into tuberculin syringes at the times noted in Table 1. The blood samples were transferred to cotton pads contained in combustion cups, weighed, frozen on dry ice, and stored frozen until time of assay by combustion analysis. Plasma samples were processed from rats in Groups 2-3A by refrigerated centrifugation and the plasma added to chilled scintillation vials for analysis by LSC.

Following the four-hour exposure, the rats in Group 1 were euthanized by sodium pentobarbital injection and as much whole blood as possible was withdrawn from the catheter. The exposure atmosphere was flushed out of the exposure bag and into a charcoal trap. Tygon tubing was connected to the valve of each polypropylene port and the valves opened. One valve, serving as the inlet port, was connected to an air line, and the other valve, serving as the outlet, was connected to a charcoal trap. A vacuum pump was used to draw air out of the exposure bag. After several air exchanges, the lines were turned off and the bag opened. The carcass was removed and frozen in dry ice to prevent volatilization of the test material. The carcasses were stored frozen until time on analysis.

Following exposure of Group 2-3A rats, the exposure bags were evacuated as described for Group1 rats and the rats removed and placed into individual plastic metabolism cages. Excreta were collected from the exposure bag and were collected over dry ice for 20-hours post-exposure from the metabolism cage. Urine volumes were recorded and triplicate aliquots were analyzed by LSC. The remaining urine was stored frozen.

The urine funnels were rinsed and the funnel washes kept separate from their respective urine samples. The wash volumes were recorded and triplicate aliquots were analyzed. The metabolism cage system was rinsed after urine collection with methanol followed by distilled water. The rinses were combined and the volumes recorded. Triplicate aliquots of the cage wash were analyzed by LSC.

The feces were collected into tarred containers, weighed, and stored frozen. A 25% homogenate in water of each sample was prepared and aliquots analyzed in triplicate by combustion analysis.

Twenty hours after exposure, the rats in Groups 2-3A were euthanized with sodium pentobarbital and as much whole blood withdrawn as possible. Limited necropsies were done on each animal and the liver, kidney, spleen, lung and fat were collected. The organ samples were weighed, frozen in liquid nitrogen, and stored frozen until analysis by combustion. The carcass of each animal was frozen in dry ice and stored frozen until analysis. The frozen carcasses were chopped into smaller sections and homogenized. Frozen aliquots of the homogenates were weighed and analyzed by combustion.
The carcasses of the two control rats were treated similarly to the carcasses of rats in Groups 2-3A.

c. Metabolite characterization studies: Metabolite characterization studies were not done.

3. Statistics: Statistical analyzes were limited to the determination of the mean and standard deviation.

II. RESULTS:

A. PHARMACOKINETIC STUDIES:

1. Average exposure concentration: Shown in Table 2 are the average 1-MCP exposure concentrations to male and female rats over four hours. All results were within 14% of nominal.

TABLE 2. Average concentration of 1-MCP in atmosphere to male and female rats exposed for four hours.

Group	Sex	Number	Nominal (ppm)	Actual (ppm)	Percent of nominal	Percent of Target Dose[a]
1	Male	4	1000	1042 ± 24.5	104	107.2 ± 1.5
1	Female	2	1000	994 ± 78.8	99.4	102.3 ± 4.6
2	Male	3	100	103 ± 15.3	103	111.2 ± 15.9
2	Female	3	100	87 ± 8.3	87	91.8 ± 8.9
3	Male	3	1000	1078 ± 55.9	108	109.9 ± 5.74
3	Female	3	1000	1007 ± 51.9	101	102.9 ± 4.1

Data derived by reviewer from pages 97-102 of MRID 47088616
[a]Represents the total dose of radiolabeled 1-MCP the rats were exposed to.
Groups 3 and 3A are presented combined

2. Exposure assumptions: The approximate volume of the exposure bags when fully expanded was 30L. Assuming a rat weighing between 200 and 300 grams breathes at a rate of 0.2 L/min, the rat would inhale/exhale approximately 48 liters of air, or approximately 1.6 times the volume in the bag, during the four-hour exposure.

3. Absorption: If assumed that the percent of dose recovered in the carcass, tissue, and excreta represents absorbed test material, then rats exposed to 100 ppm (Group 2) test material had ~5% of the absorbed dose (males 6%, females 4%) while rats exposed to 1000 ppm (Group 3) had ~1.9% (males 2.4%, females 1.4%) 20 hours after treatment (Table 3). No significant sex-related differences in absorption were found. The administered dose (~1.6%) could be considered absorbed by male and female rats exposed to 1000 ppm (Group 1) with four hours of exposure.

TABLE 3. Percent of ^{14}C-1-MCP dose recovered from each fraction after four hours inhalation exposure						
Group	**Sex**	**Carcass**	**Tissue[a]**	**Excreta**	**Chamber Air**	**Total Recovery**
Group 1 (1000 ppm)	Male	1.6	--	--	89.0	90.8
	Female	1.5	--	--	98.7	100.4
	Average	1.6	--	--	93.9	95.6
Group 2 (100 ppm)	Male	1.4	0.3	4.3	84.5	90.6
	Female	1.0	0.2	2.8	87.6	91.6
	Average	1.2	0.2	3.6	86.1	91.1
Group 3 (1000 ppm)	Male	0.6	0.1	1.7	92.6	94.7
	Female	0.3	0.1	1.0	92.4	93.9
	Average	0.5	0.1	1.4	92.5	94.3

Data derived by reviewer from page 132 of MRID 47088616
[a] Includes liver, kidney, spleen, and lung
Groups 3 and 3A are presented combined

4. **Tissue distribution**: As shown in Table 4, tissue accumulation of the radiolabel was low regardless of exposure concentration or sex. No significant tissue deposition site for the radiolabel was found.

TABLE 4. Distribution of radiolabel (percent of dose) in tissues 20 hours after inhalation treatment with 1-MCP							
Group	**Sex**	**Liver**	**Kidney**	**Spleen**	**Lung**	**Tissue**	**Carcass**
Group 2 (100 ppm)	Male	0.07	0.05	0.03	0.010	0.24	1.44
	Female	0.06	0.05	0.03	0.04	0.18	1.05
Group 3 (1000 ppm)	Male	0.02	0.02	0.01	0.02	0.07	0.54
	Female	0.01	0.01	0.01	0.01	0.04	0.35

Data derived by reviewer from pages 37 and 41 of MRID 47088616
Groups 3 and 3A are presented combined

5. **Toxicokinetics:** The concentrations of ^{14}C-1-MCP in whole blood and plasma during and after exposure to the radiolabeled test material are shown in Table 5. Absorption of the radiolabeled test material was low during the exposure period and decreased upon removal of the animal from the exposure chamber. Radiolabel was detected in the whole blood and plasma within 15 minutes of the start of exposure in high-dose male and female rats. During exposure to 1000 ppm radiolabeled test material (Group 1), the whole blood concentration steadily climbed in a linear fashion reaching a peak of ~10.9 and 9.8 µg/g by the end of exposure in males and females, respectively. In Group 2 male and female rats, the concentration of radiolabel in the blood and plasma was similar, suggesting similar absorption between the sexes at both exposure concentrations (Table 5). In addition, similar T_{max}, C_{max}, and $T_{½}$ were found between the sexes (Table 6). Group 3 results for T_{max}, C_{max}, and $T_{½}$ were also similar between the sexes although a bi-phasic elimination pattern was suggested in female rats (Tables 5 and 6). The difference between the AUC of the two exposure groups suggests that absorption was approaching saturation at 1000 ppm. The relatively long T½ in both sexes at both exposure concentrations suggests that elimination is slow.

TABLE 5. Concentration of radioactivity in plasma and whole blood of male and female rats exposed by inhalation to ^{14}C-1-MCP

Group	Matrix	Sex	Hour of exposure						Hours after exposure		
			0.25	0.50	1	2	3	4	4	8	20
Group 1 (1000 ppm)	Whole Blood	Male	3.8760 (9.2)	4.6251 (11.0)	5.9579 (14.2)	7.4833 (17.8)	9.1491 (21.8)	10.9172 (26.0)	-	-	-
Group 1 (1000 ppm)	Whole Blood	Female	4.1998 (10.1)	5.1492 (12.3)	5.7916 (13.9)	7.7946 (18.7)	8.9911 (21.5)	9.8431 (23.6)	-	-	-
Group 2 (100 ppm)	Plasma	Male	-	-	1.719(14.0)	2.1521 (17.6)	2.1452 (17.5)	2.5785 (21.1)	2.2339 (18.2)	-	1.4169
		Female	-	-	1.3199 (14.9)	1.5257 (17.2)	1.7229 (19.4)	1.9595 (22.1)	1.3307 (15.0)	--	1.0126 (11.4)
Group 2 (100 ppm)	Whole Blood	Male	-	-	1.1032 (13.2)	1.4736 (17.6)	1.7592 (21.0)	1.9625 (23.4)	1.335 (15.9)	-	0.7514 (9.0)
		Female	-	-	1.2279 (14.3)	1.5617 (18.2)	1.8262 (21.2)	2.0662 (24.0)	1.2259 (14.2)	-	0.6954 (8.1)
Group 3 (1000 ppm)	Plasma	Male	4.0684 (5.6)	5.907 (8.2)	6.3079 (8.7)	7.2458 (10.0)	10.0425 (13.9)	10.8923 (15.1)	8.9872 (12.4)	9.3664 (12.9)	9.5540 (13.2)
		Female	NS	NS	4.8750 (10.3)	6.0636 (12.8)	7.7216 (16.3)	10.1165 (21.4)	9.9893 (21.1)	NS	8.5168 (18.0)
Group (1000 ppm)	Whole Blood	Male	3.9813 (6.4)	5.2058 (8.3)	6.2722 (10.0)	8.7395 (13.9)	10.0437 (16.0)	11.1998 (17.9)	6.4541 (10.3)	6.2462 (10.0)	4.5539 (7.3)
		Female	NS	NS	6.2983 (13.5)	8.0740 (17.4)	9.6260 (20.7)	10.8793 (23.4)	6.9212 (14.9)	NS	4.6946 (10.1)

Data derived by reviewer from pages 34-35 and 38-39 of MRID 47088616
Results expressed as µg equivalent of ^{14}C-1-MCP/g matrix with percent of total recovered in parenthesis
NS = Not sampled
Groups 3 and 3A are presented combined

TABLE 6. Toxicokinetic parameters of male and female rats exposed to 1-MCP for four hous

Group	Matrix	T_{max} (Hours)	C_{max} (ppm)	$T_{½}$ (Hours)	AUC (ppm*hr)	T_{max} (Hours)	C_{max} (ppm)	$T_{½}$ (Hours)	AUC (ppm*hr)
		Male				Female			
Group 2 (100 ppm)	Plasma	4	2.58	23.5	45.3	4	1.96	24.4	30.2
	Whole Blood	4	1.96	15.6	28.1	4	2.07	14.2	27.0
Group 3 (1000 ppm)	Plasma	4	10.9	14.4	220	4	10.1	ND	210
	Whole Blood	4	11.2	5.0	157	4	10.9	6.1/18.8[a]	155

Data from pages 106-107 of MRID 47088616
[a]Initial phase/Overall
ND = An accurate value could not be determined
Groups 3 and 3A are presented combined

6. <u>Excretion:</u> The urinary and fecal excretion of ^{14}C-1-MCP is shown in Table 7. Both sexes of animals in both exposure groups eliminated the radiolabeled test material predominately in the urine with elimination in the feces secondary. Elimination in the excreta was <5% of the administered dose over the 24-hour study period, implying absorption was minimal.

TABLE 7. Urinary and fecal excretion (percent of dose) of radiolabeled 1-MCP in male and female rats					
Group	**Sex**	**Time**	**Urine**	**Feces**	**Ratio**
Group 2 (100 ppm)	Male	0-4	1.34	0.57	2.35
		4-24	2.03	0.38	5.34
		0-24	3.37	0.96	3.51
Group 2 (100 ppm)	Female	0-4	0.92	0.28	3.29
		4-24	1.40	0.20	7.00
		0-24	2.31	0.48	4.81
Group 3 (1000 ppm)	Male	0-4	0.77	0.06	12.8
		4-24	0.75	0.14	5.36
		0-24	1.51	0.20	7.55
Group 3 (1000 ppm)	Female	0-4	0.28	0.04	7.00
		4-24	0.58	0.10	5.80
		0-24	0.86	0.15	5.73

Data from page 108 of MRID 47088616
Groups 3 and 3A are presented combined

B. METABOLITE CHARACTERIZATION STUDIES:

Metabolite identification studies were not done.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS= CONCLUSIONS:

The study author concluded that 1-MCP appears rapidly in the blood stream when inhaled by the rat. Following exposure, 1-MCP is cleared from the blood compartment at a modest rate. Minimal amounts of the material were present in the tissues or carcass and were eventually excreted via the urine and feces. There was no evidence that 1-MCP bioaccumulates in the body. Overall, the findings suggest that the molecule is inhaled and exhaled by the rat unchanged.

B. REVIEWER COMMENTS:

In this study, male and female Crl:CD®BR were exposed to concentrations of 100 ppm or 1000 ppm radiolabeled 1-MCP for four hours. Absorption was similar between the sexes within exposure groups with rats exposed to 100 ppm having ~5% of the dose in the tissues or excreta (males 6%, females 4%) while rats exposed to 1000 ppm had ~1.9% (males 2.4%, females 1.4%) 20 hours after exposure. Tissue distribution was also similar between sexes within exposure groups; with specific tissue accumulation <0.5% and residual carcass concentrations <2% at both exposure concentrations. No bioaccumulation was noted. Concentrations of the radiolabel in the excreta were low, also implying limited absorption, but were higher in the urine by a factor of 2-12 dependent on exposure concentration. No significant differences in elimination were found between the sexes with exposure groups.

^{14}C-1-MCP was detectable in the whole blood (Groups 1 and 3) and plasma (Group 3) of male and female rats within 15 minutes during the four-hour exposure. During exposure, concentrations of the radiolabel generally increased in a linear fashion and peaked after four hours. The concentrations of the radiolabeled test material in the whole blood and plasma of male and female rats were low in both exposure groups, and decreased with the cessation of exposure. In Group 2 male and female rats, the concentration of radiolabel in the blood and

plasma was similar, implying similar absorption. In addition, similar T_{max}, C_{max}, and $T_{½}$ were found between the sexes. The results between whole blood and plasma values suggest that the radiolabeled test material was carried in the plasma with little binding to the red blood cell. Group 3 results for T_{max}, C_{max}, and $T_{½}$ were also similar between the sexes although a bi-phasic elimination pattern was suggested in females. The difference in AUC between the two exposure groups suggests that absorption was approaching saturation at 1000 ppm. The relatively long $T_{½}$ in both sexes at both exposure concentrations suggest that elimination is modest.

No assumptions on the metabolic disposition of the test material can be made based on the study results.

C. CONCLUSIONS

The submitted toxicokinetic study is not satisfying data requirement under OPPTS guideline 870.7485. Metabolite identification studies were not conducted. The animals were observed and excreta collected over a 20-hour period rather than the recommended seven days. Because of the low absorption of the test material, however, the study duration could be considered acceptable. The study report appears to be presented from various modifications conducted over a period of years. References to later additions to the report were not included in the summary or conclusions of the study report. However, the study will not affect the conclusion of risk assessment for this registration.